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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/774,490	JIN, SHENGFANG	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *23-27 and 29-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *23-27 and 29-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 5-22 and 28 have been canceled. Claim 23 has been amended. Claims 29-50 have been added. Claims 23-27 and 29-50 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claims 23-27 and 29-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

The claims encompass the gene encoding the protein encoded by SEQ ID NO:1. The specification has identified SEQ ID NO:1 as a polynucleotide which is upregulated in drug resistant EMT-6 cells (Teicher et al, Science, 1990, Vol. 247, pp. 1457-1461). The claims are drawn to a gene which encodes the protein encoded by SEQ ID NO:1. It is recognized in the art that a eukaryotic gene includes regulatory regions and non-coding regions (Rieger et al, Glossary of Genetics, 1991, page 190, lines 15-28) which affect the level of the expressed polypeptide. The specification has not disclosed the portion of the gene which affects the expression of SEQ ID NO:1 when the cell is in a drug resistant versus drug susceptible state. It is well known in the art that that the description of an expressed polynucleotide is commensurate with a mRNA, and that the sequence of a mRNA provides no information as to the structure of the complete gene involving the sequence of enhancers, promoters and introns, from which the mRNA is processed. The art recognizes that the structure of a gene is empirically determined. for example, the untranslated regulatory and structural elements of a gene mediating the expression of a housekeeping protein or a protein which is tissue specific would be expected to be much different from the structure of the instant gene encoding the protein encoded by the mRNA or cDNA of SEQ ID NO:1. Thus, the description of an expressed polynucleotide does not fulfill the description of a "gene". One of skill in the art would reasonably conclude that applicant was not in possession of the isolated gene.

Claims 23-27, and 29-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention..

(A) As drawn to methods which encompass anti-sense nucleic acids

The instant invention has disclosed the correlation between the expression of SEQ ID NO:1 in a cell and the resistance of said cell to drugs. The instant claims are drawn to a method for determining whether a test compound is a candidate compound for modulating drug resistance of an eukaryotic cell the method comprising determining the level of expression of a gene comprising the nucleotide sequence of SEQ ID NO:1 in a eukaryotic cell in the presence and the absence of a test compound and identifying the compound as a candidate modulator of drug resistance of the eukaryotic cell if the level of expression of the gene in the eukaryotic cell in the presence of the test compound differs from the level of expression of the gene in the absence of the test compound. The specification states on page 2, line 31 to page 3, line 10, that the instant invention provides for agents which inhibit or stimulate the activity of the resistance protein or expression. Thus the claims are broadly drawn to encompass the candidate compounds for the upregulation and downregulation or drug resistance. The specification suggests that an antibody which specifically binds to the protein or a antisense nucleic aid can be the used to treat a subject having a drug resistance cancer. The specification teaches that a resistance modulator can be a resistance protein or nucleic acid. Thus, the specification is teaching candidate compounds which include the SEQ ID NO:1 and the protein encoded thereby. There are no teachings in the specification nor any art of record which identify a disease or condition which would benefit from the upregulation of SEQ ID NO:1 and the concomitant increase drug-efflux One of skill in the art would not know how to use a candidate compound identified by the instant method for therapeutic purposes without the identification of a pathological condition which would benefit from the administration of the test compounds which upregulate the activity or expression of SEQ ID NO:1. .The specification does not disclose or suggest any other compounds beyond nucleic acids and the protein encoded thereby for the modulation of the resistance gene. Further, the specification is not enabling for how to use antisense nucleic acids or nucleic acids encoding SEQ ID NO:1 in the treatment of drug-resistant cancers or any other disease. The transfer of an antisense construct or vector comprising SEQ ID NO:1 into a patient is in the realm of gene therapy which is unpredictable for the reasons set forth below.

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) that clinical efficacy had not been definitively demonstrated with any gene therapy

protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that in 1995 current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

(B) As drawn to the expression of a gene encoding the protein expressed by SEQ ID NO:1 wherein the gene is not an endogenous gene.

Further, claims 27, 38 and 46 are specifically drawn to methods 23, 33 and 34, wherein the gene is not an endogenous gene. Thus, claims 23-25, 27, 29-36, 38-44 and 46-50 encompass method wherein the gene is not an endogenous gene. It is well recognized in the art that expression of eukaryotic genes is regulated by regulatory regions located within the non-expressed portion of the genome, and which include regions within the promoter, the introns and enhancer regions which are not necessarily proximate to the expressed gene (Rieger et al, Glossary of Genetics, 1991, page 190, lines 15-28, page 479, last line to page 480, line 12). The specification has provided the sequence of the polynucleotide of SEQ ID NO:1. The claims encompass other polynucleotide which encode the protein encoded by SEQ ID NO:1 and therefore include degenerate coding sequences of SEQ ID NO:1. It is reasonably concluded that if the expression of SEQ ID NO:1 were under the control of a promoter commonly used in recombinant expression in eukaryotic cells, such as the CMV promoter, that said expression would be invariant, because the promoter would not respond to the presence or absence of drugs within the cell. The specification has not disclosed the regulatory regions which control the expression of SEQ D NO:1, and thus, one of skill in the art would be subject to undue experimentation in order to locate and isolate the regulatory sequences controlling the expression of SEQ ID NO:1 within the genomic DNA of the EMT-6-tumor derived cells in order be able to recombinantly express SEQ ID NO:1 under control of the critical regulatory regions necessary

for the downregulation or upregulation of SEQ ID NO:1. It is concluded that the specification is not enabling for the to practice the claimed invention in a cell which is not an EMT-6 derived cell.

Applicant argues that the claimed methods are enabled because they are draw to methods of screening and not therapeutic agents or methods. This has been considered but not found to be persuasive. In order for the claimed methods to be fully enabled one of skill in the art would necessarily be able to not only identify the candidate molecules through the claimed screening method, but be able to use said candidate molecules as therapeutic agents or in therapeutic methods. Without this criterion, the instant invention would be lacking in specific and substantial utility.

Applicant argues that there is enablement for agents which increase the drug resistance or normal cells to protect said normal cells from the toxic effect of chemotherapy. however, the specification is not enabling for how to administer such candidate agents. One of skill in the art would know that local administration of an agent to a tumor site would concentrate said agent at the tumor site for a limited time. however, administration of an agent which acts to increase the drug resistance of a cell to the tumor site would necessarily be taken up by the tumor as well as the normal cell surround the tumor and act to increase the drug resistance of the tumor in addition to the drug resistance of the normal cells surround in the tumor. Conversely, if the agent which increased the drug resistance of a cell were administered systemically, said agent would also reach the tumor by way of the tumor vasculature. Thus, it appears that one of skill in the art would be subject to undue experimentation in order to use the candidate modulators which increase the drug resistance of a cell.

Applicant argues that the specification discloses a wide variety of compounds that can be screened to identify candidate modulators of drug resistance such as peptide, petidomimetics and small molecules which can bind to or modulate the activity or expression of the disclosed polypeptide, and that this is a separate enablement issue from how to make and use anti-sense nucleic acids in gene therapy. This has been considered but not found persuasive. It is noted that the instant claims all specify that the level of expression of SEQ ID NO:1 is modulated,

decreased or increased. The instant claims do not encompass screening for agent which affect the activity of SEQ ID NO:1 beyond affecting the expression of SEQ ID NO:1. Enablement is a two-pronged test: how to make and how to use. The instant disclosure teaches a method of making candidate modulators by screening the expression of SEQ ID NO:1, however, it is not enabling for how to use the plethora of candidate modulators. identified by the screen Without this enablement, the method produces candidate modulators which require further experimentation before it is determined if and how said candidate modulator can be used in a therapeutic method. therefore, on of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to used the majority of candidate modulators identified by the instant method claims. Applicant states that despite the fact that very few compounds identified in target-based screens ultimately prove to be a successful drug, many companies spend time and resources to screen candidate drugs. Applicant argues that the examiner cannot simply dismiss a scientific approach that s so widely used simply because the ultimate goal of the whole of the therapeutic discovery process is difficult to achieve.
this has been considered but not found persuasive. The scope of a claim must be commensurate with the scope of enablement set forth. the claims thus encompass methods which, by applicants own admission, produce a majority of candidate modulators which will ultimately not be useful in therapeutic protocols. thus, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the claimed candidate modulators.
112, 2nd

The recitation of "candidate modulator" in claims 39 and 40 lacks antecedent basis in claim 33. The recitation of "candidate modulator" in claims 47 and 48 lacks antecedent basis in claims 34.

It is unclear how claim 39 and 40 further limit claim 33, and it is unclear how claims 47 and 48 further limit claim 34. Claim 33 contains the specific embodiment of decreasing the level of expression of "the gene" by the candidate compounds. thus the specific embodiment of claim 39 does not further limit claim 33, and the specific embodiment of claim 40 appears to conflict with the limitations of claim 33. Claim 34 contains the specific embodiment of increasing the level of expression of "the gene" by the candidate compounds. thus the specific

embodiment of claim 44 does not further limit claim 34, and the specific embodiment of claim 44 appears to conflict with the limitations of claim 34.

All other rejections and objections as set forth in the previous Office action are withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (571) 272-0828. The examiner can normally be reached on Monday through Friday from 9 am to 6:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (571) 272-0871. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service at 703-308-4357.

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02/17/04

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